REMARKS

The Examiner rejected claims 27-58. Claim 44 has been cancelled herein without prejudice. Thus, claims 27-43 and 45-58 remain pending. Claim 27 has been amended to indicate that the monitored gene expression is gene expression of virally encoded nucleic acid. Claim 43 have been amended to incorporate the language of claim 44. Applicants' specification fully supports these amendments. For example, page 9, lines 27-28 disclose monitoring as referring to a process of determining the amount of viral gene expression. Thus, no new matter has been added.

Applicants respectfully request entry of the above amendments, which raise no new issues that would require further consideration and/or search, and which place the application in better condition for allowance.

Sequence Listing

Under separate cover, Applicants have filed a Response to the Notice to Comply. The specification is in compliance with the requirements of 37 C.F.R. §§ 1.822 and/or 1.823.

Examiner Interview

Applicant's agent thanks Examiner Chen for the courtesy of the telephonic interview on April 22, 2003, with Patrick Finn. The substance of this telephonic interview involved the rejections and claim amendments presented herein. In addition, two recent journal publications authored by the inventor's research group: Peng *et al.*, *Nature Medicine*, 8:527-531 (2002) and Peng *et al.*, *Cancer Res.*, 62:4656-4662 (2002), were discussed. Copies of these references are attached hereto for the convenience of the Examiner.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 27-42 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner questioned the meaning of the phrase "monitoring gene expression" as set forth in claim 27.

Claim 27 has been amended to indicate that the monitored gene expression is gene expression of virally encoded nucleic acid. A person having ordinary skill in the art at the time Applicants filed would have understood the meaning of claim 27 as amended. Thus, claim 27 is clear and unambiguous.

In light of the above, Applicants respectfully request withdrawal of the rejections of claims 27-42 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 27-58 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Specifically, the Examiner stated that if gene expression refers to genes other than the gene encoding the heterologous polypeptide, then:

> it is unclear how the gene is connected to the gene encoding said heterologous polypeptide. The specification fails to provide the correlation between the gene whose expression in going to be monitored and the gene encoding the heterologous polypeptide. The specification also fails to provide adequate guidance and evidence for how detecting the amount of the heterologous polypeptide in a biological fluid from an organism could provide an indication of the amount of a gene expression.

In addition, the Examiner appears to assert that virus administered intratumorally or locally into the brain will likely stay in the tumor or brain.

Applicants respectfully disagree. Applicants' specification fully enables present claims 27-43 and 45-58. Claim 27 requires the recited Paramyxoviridae virus to contain nucleic acid encoding the heterologous polypeptide. Claim 27 also indicates that the method involves monitoring gene expression of virally encoded nucleic acid. As explained during the April 22, 2003 telephonic interview, Paramyxoviridae viruses have a particular genome structure that results in a gradient of viral gene expression. This is also explained in section 4 on page 26 of Applicants' specification. In fact, this section discusses the relationship between expression of a heterologous polypeptide encoded by a sequence inserted into a virus and other viral coding units. For example, page 26, lines 18-19 state that the "further the coding unit is from the viral

promoter, the lower will be the expression." In addition, page 28, lines 5-13 disclose methods for calibrating the amount of heterologous polypeptide detected to the amounts of other viral products.

With respect to the Examiner's assertion that virus administered intratumorally or locally into the brain will likely stay in the tumor or brain, Applicants' respectfully submit the following. First, no evidence has been cited to support this assertion. In addition, according to the Peng *et al.* reference (*Cancer Res.*, 62:4656-4662 (2002)), serum levels of a virally encoded marker peptide (soluble human carcinoembryonic antigen) was used to "easily follow the kinetic profile of viral gene expression." See, Abstract on page 4656. The virus was injected directly into large established subcutaneous tumors. See, Abstract and first full paragraph on page 4659.

Taken together, a person having ordinary skill in the art at the time Applicants filed would have been able to follow Applicants' extensive teachings to monitor gene expression of virally encoded nucleic acid as presently claimed without undue experimentation. Thus, claims 27-43 and 44-58 are fully enabled.

In light of the above, Applicants respectfully request withdrawal of the rejections of claims 27-43 and 45-58 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. §§ 102(b) and 103(a)

The Examiner rejected claims 43, 53, 54, and 58 under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over the Kirn *et al.* reference (*Mol. Med. Today*, 2(12):519-527 (1996)).

Applicants respectfully disagree. To further prosecution, however, claim 43 has been amended to recite the language of claim 44. Thus, claim 43 as amended is patentable over the Kirn *et al.* reference.

In light of the above, Applicants respectfully request withdrawal of the rejections of claims 43, 53, 54, and 58 under 35 U.S.C. §§ 102(b) and 103(a).

Rejections under 35 U.S.C. § 102(a)

The Examiner rejected claims 43, 44, 53, 54, and 56 under 35 U.S.C. § 102(a) as being anticipated by the Singh *et al.* reference (*J. Gen. Virol.*, 80:101-106 (1999)). Specifically, the Examiner stated that:

> Singh teaches generation of a measles virus (MV) that expresses biologically active human IL-12 by inserting the coding sequence of the two subunits of human IL-12 separated by an IRES and between H and L genes of MV (e.g. abstract, Fig. 1). Singh also teaches making a recombinant MV expressing marker genes such as green fluoroesence protein (GFP), beta-galactosidase and chloramphenicol acetyltransferase (CAT), which are biologically inactive (e.g. p. 103). IL-2 [sic], GFP, beta-galactosidase and CAT are heterologous polypeptides. Thus, claims 43, 44, 53, 54 and 56 are anticipated by Singh.

Applicants respectfully disagree. Claim 43, as amended, recites a Paramyxoviridae virus having a nucleic acid sequence encoding a heterologous polypeptide. Claim 43 also recites that the heterologous polypeptide (1) is released from the infected cells into a biological fluid of the organism when expressed and (2) is biologically inactive in the organism. At no point does the Singh *et al.* reference disclose such a Paramyxoviridae virus. In fact, none of the viruses disclosed in the Singh *et al.* reference contain a nucleic acid sequence encoding a heterologous polypeptide that is both (1) released from the infected cells into a biological fluid of the organism when expressed and (2) biologically inactive in the organism. IL-12, GFP, beta-galactosidase, and CAT are polypeptides that are biologically active and/or not released from infected cells into a biological fluid. Thus, claim 43, as amended, is not anticipated.

In light of the above, Applicants respectfully request withdrawal of the rejections of claims 43, 53, 54, and 56 under 35 U.S.C. § 102(a).

CONCLUSION

Applicants submit that claims 27-43 and 45-58 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned agent at the telephone number below if such will advance prosecution of this application. The Commissioner is

authorized to charge any fees or credit any overpayments to Deposit Account No. 06-1050.

Attached is a marked-up version of the changes being made by the current amendment

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claim 44 has been cancelled without prejudice.

Claims 27 and 43 have been amended as follows:

27. (Amended Once) A method of monitoring gene expression of virally encoded nucleic acid from virus infected cells within an organism, said method comprising:

(a) administering a Paramyxoviridae virus to said organism, wherein said Paramyxoviridae virus comprises a nucleic acid sequence encoding a heterologous polypeptide, and wherein said heterologous polypeptide is released from infected cells into a biological fluid of said organism when expressed, and

(b) detecting the amount of said heterologous polypeptide in said biological fluid, thereby providing an indication of the amount of said gene expression.

43. (Amended Once) A Paramyxoviridae virus comprising a nucleic acid sequence encoding a heterologous polypeptide, wherein said Paramyxoviridae virus infects cells of an organism when administered to said organism, and wherein said heterologous polypeptide is released from said infected cells into a biological fluid of said organism when expressed, said released heterologous polypeptide being detectable in said biological fluid, and wherein said heterologous polypeptide is biologically inactive in said organism.